Remarks

Reconsideration and withdrawal of the rejections of the claims, in view of the amendments and remarks herein, is respectfully requested.

Claims 1, 19 and 58-59 are amended, and claims 60-67 are added. The amendments are intended to advance the application and are not intended to concede to the correctness of the Examiner's position or to prejudice the claims prior to amendment, which claims are present in a continuation of the above-identified application. No new matter has been added. Claims 1-3, 8-11, 19-21, 23-37, 41-43, 46-54, and 58-67 are now pending.

The amendments to the claims, and new claims 60-61, are supported by originally-filed claim 19 (a recombinant AAV vector comprising at least one heterologous transcriptional regulatory element functional in a host cell and which does not comprise sequences which encode a protein), page 6, line 26-page 7, line 8 (the use of two AAV vectors for gene therapy, one of which has an enhancer and/or promoter and the other of which has an open reading frame of interest), page 10, lines 17-20 (enhancement of transgene expression was also achieved by *cis*-activation of ITRs in vectors without a promoter), page 87, lines 25-26 (one of the vectors, AV.Luc contains the luciferase transgene and SV40 poly A signal but no promoter), and page 88, lines 27-28 (AV.Luc contains no heterologous promoter sequences), and Figures 19 and 20-21 in the specification.

New claims 62-67 are supported by originally-filed claims 3 and 8.

The Examiner is thanked for the courtesies extended to Applicant's Representative in the telephonic interview conducted on May 16, 2005 in which proposed claim amendments in view of the cited art were discussed.

Claims 57 and 58 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is respectfully traversed.

Applicant discloses the use of AAV vectors for "*cis*-activation" (see, for instance, page 10, lines 9-20 and Figures 20-21), i.e., a regulatory element(s) in one rAAV vector that is introduced into cells can regulate in *cis* expression of a transgene delivered by another rAAV, which is in contrast to "*trans*-splicing," i.e., the use of splicing vectors (page 91, lines 9-18 and

Figures 19 and 25). For instance, at page 6, line 26-page 7, line 8 of the specification, it is disclosed that, with respect to gene therapy with rAAV, large regulatory elements and genes beyond the packaging capacity of rAAV can be brought together by co-infecting with two independent rAAV vectors. It is disclosed that in one embodiment, one vector has an enhancer and/or a promoter and the other vector has an open reading frame of interest with or without a minimal promoter ("*cis*-activation"). After coinfection with the two vectors, it is disclosed that transgene size in increased beyond that for a single AAV vector and the open reading frame is linked to the enhancer and/or promoter (page 7, lines 3-6). In another embodiment, it is disclosed that vectors encoding two independent regions of a gene are brought together to form an intact splicing unit ("*trans*-splicing"; page 7, lines 6-8). At page 91, it is disclosed that through concatamerization, two vectors for *trans*-splicing or for *cis*-activation are brought together allowing for splicing or *cis*-activation of enhancer/promoter combinations. Figures 19 and 21 exemplify the two approaches to bring genetic elements together using rAAVs.

Accordingly, one of skill in the art in possession of Applicant's specification is clearly apprised of two different approaches to deliver "large" genetic elements to cells via rAAV vectors, one that relies on placing portions of genes and splice sites at appropriate locations in each vector to allow for splicing to bring portions of the gene together, and another that does not rely on splicing. Therefore, withdrawal of the § 112(1) rejection is appropriate and is respectfully requested.

The Examiner rejected claims 1, 9, 46-47, and 55-56 under 35 U.S.C. § 102(e) as being anticipated by Engelhardt et al. (U.S. Patent No. 6,436,392). The Examiner further rejected claims 1, 9, 19-20, 46-47, 55-56, and 58 under 35 U.S.C. § 102(b) as being anticipated by Rendahl et al. (Nature Biotechnology, 16:757 (1998)). These rejections, as they may be maintained with respect to the pending claims, are respectfully traversed.

It is disclosed in the '392 patent that rAAV vectors, each containing a promoter and an open reading frame between ITRs, may become linked after infection of the host cell with the vectors and synthesis of double-stranded viral DNA (column 4, lines 41-56 and column 5, lines 26-38). Other vectors disclosed in the '392 patent include rAAV vectors that contain an open reading frame flanked by a splice site, i.e., one rAAV vector contains a splice acceptor site and another rAAV vector contains a splice donor site, which vectors together encode a functional

gene product (column 4, lines 57-column 5, line 25). It is disclosed that transcription of a molecule formed by linking the two rAAVs in a cell results in a spliced RNA molecule which encodes a functional peptide (column 49, lines 14-22).

In neither embodiment disclosed in Engelhardt et al. does the non-ITR promoter in one rAAV vector regulate transcriptional expression of a functional gene product encoded by the other rAAV vector. Thus, Engelhardt et al. do not teach Applicant's invention.

The Rendahl et al. article discloses two rAAV vectors, one having a tetracycline sensitive operator sequence linked to a minimal CMV promoter which controls expression of a murine erythropoietin (epo) transgene (rAAV-(tetO)7-minCMV-mEPO), and the other having a CMV promoter controlling expression of a tetracycline responsive transactivator, tTA (abstract and Figure 1, rAAV-CMV-tTA), i.e., it is an operon like system. The two rAAVs were coinjected directly into the skeletal muscle of adult immunocompetent mice (abstract). It is disclosed that transcription of the murine erythropoietin transgene was controlled by systemic administration or withdrawal of tetracycline over an 18 week period, demonstrating that the two vectors were capable of transducing the same cell (abstract). Note that the CMV promoter in the vector encoding tTA does not regulate transcription of murine erythropoietin (mepo). Rather, the minimal CMV promoter present in the same vector as the murine epo open reading frame controls transcription of erythropoietin. Accordingly, Applicant's invention is not disclosed in Rendahl et al.

Therefore, withdrawal of the § 102 rejections is respectfully requested.

The Examiner rejected claims 1, 9, 46-47, and 55-56 under the judicially created doctrine of obviousness-type double patenting over claims 8-15 of U.S. Patent No. 6,436,392. This rejection is respectfully traversed.

Claim 8 of the '392 patent is directed to a method to express a polypeptide in a host cell. The method comprises contacting a host cell comprising a first AAV vector comprising linked: i) a first DNA segment comprising a 5'-inverted terminal repeat (ITR) of AAV; ii) a second DNA segment comprising a splice acceptor site; iii) a third DNA segment comprising a portion of an open reading frame for a polypeptide; and iv) a fourth DNA segment comprising a 3'-ITR of AAV; with a second AAV vector comprising linked: i) a first DNA segment comprising a 5'-ITR of AAV; ii) a second DNA segment comprising a splice donor site; iii) a third DNA

segment comprising a portion of an open reading frame which together with the DNA segment of (a)(iii) encodes a functional polypeptide; and iv) a fourth DNA segment comprising a 3'-ITR of AAV so as to yield a host cell which expresses the functional polypeptide.

Claim 9 of the '392 patent is directed to a method to express a polypeptide in a host cell, comprising: contacting a host cell with a first AAV vector comprising linked: a) i) a first DNA segment comprising a 5'-ITR of AAV; ii) a second DNA segment comprising a portion of an open reading frame operably linked to a promoter; iii) a third DNA segment comprising a splice donor site; and iv) a fourth DNA segment comprising a 3'-ITR of AAV; and a second AAV vector comprising linked: b) i) a first DNA segment comprising a 5'-ITR of AAV; ii) a second DNA segment comprising a splice acceptor site; iii) a third DNA segment comprising a portion of an open reading frame which together with the DNA segment of a) ii) encodes a functional polypeptide; and iv) a fourth DNA segment comprising a 3'-ITR of AAV; so as to yield a host cell which expresses the functional polypeptide. Claims 10-15 are dependent, in part, on claims 8-9.

Claims 8-15 of the '392 patent do not disclose or suggest a composition comprising at least two rAAVs, wherein one of the rAAVs comprises an entire open reading frame and the other rAAV comprises at least one *cis*-acting heterologous transcriptional regulatory element which regulates transcription of the gene product encoded by the open reading frame, after the host cell is contacted with the two vectors.

Hence, withdrawal of the obviousness-type double patenting rejection is appropriate and respectfully requested.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney at (612) 373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

JOHN F. ENGELHARDT ET AL.

By their Representatives,

SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A.
P.O. Box 2938
Minneapolis, MN 55402
(612) 373-6959

Date August 17, 2005 By

Janet E. Embretson
Reg. No. 39,665

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Mail Stop Amendment, Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 17 day of August, 2005.

CANDIS BUENDING

Name

Signature